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ORIGINAL REPORT

No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials

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ABSTRACT

Purpose
This study investigated the long-term probability of developing a second cancer in a large pooled cohort of patients treated with surgery with or without radiotherapy (RT).

Patients and Methods
All second cancers diagnosed in patients included in the TME, PORTEC-1, and PORTEC-2 trials were analyzed. In the TME trial, patients with rectal cancer (n = 1,530) were randomly allocated to preoperative external-beam RT (EBRT; 25 Gy in five fractions) or no RT. In the PORTEC trials, patients with endometrial cancer were randomly assigned to postoperative EBRT (46 Gy in 2-Gy fractions) versus no RT (PORTEC-1; n = 714) or EBRT versus vaginal brachytherapy (VBT; PORTEC-2; n = 427).

Results
A total of 2,554 patients were analyzed (median follow-up, 13.0 years; range 1.8 to 21.2 years). No differences were found in second cancer probability between patients who were treated without RT (10- and 15-year rates, 15.8% and 26.5%, respectively) and those treated with EBRT (10- and 15-year rates, 15.4% and 25.6%, respectively) or VBT (10-year rate, 14.9%). In the individual trials, no significant differences were found between treatment arms. All cancer survivors had a higher risk of developing a second cancer compared with an age- and sex-matched general population. The standardized incidence ratio for any second cancer was 2.98 (95% CI, 2.82 to 3.14).

Conclusion
In this pooled trial cohort of > 2,500 patients with pelvic cancers, those who underwent EBRT or VBT had no higher probability of developing a second cancer than patients who were treated with surgery alone. However, patients with rectal or endometrial cancer had an increased probability of developing a second cancer compared with the general population.

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INTRODUCTION

Cancer survivors are at increased risk of developing a second cancer compared with the general population.[1] This increased risk has been explained by several factors, such as lifestyle factors, genetic susceptibility, and administered chemotherapy or radiotherapy (RT). In a large US SEER-based study, RT was found to be related to a relatively small proportion (8%) of second cancers; most second cancers were related to other factors.[2] Increased risk for an RT-related second cancer was found with increasing time since treatment and with decreasing age at diagnosis.

During the last decades, the role of (neo) adjuvant RT for rectal and endometrial cancers has been investigated in several large trials. For both rectal and endometrial cancers, external-beam RT (EBRT) increased locoregional control, but this did not translate into an improvement in overall survival.[3-6] The benefit of EBRT for local control should therefore be balanced against the risk of adverse effects, such as long-lasting treatment-related bowel symptoms and RT-related second cancers. Several large studies have assessed the risk of a second cancer in patients treated with RT after surgery for rectal or endometrial cancer, with varying results.[7-10] Although some studies have found an increased risk of

developing a second cancer after RT,[7] especially in patients treated at younger ages,[8] others have reported that RT did not lead to overall differences in second cancer risk.[9,10]

The PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1) and PORTEC-2 and TME (Total Mesorectal Excision) trials have had a major impact on guidelines for (neo) adjuvant RT for endometrial and rectal cancers, respectively. These three randomized trials together included > 2,500 patients, with long and complete follow-up information for patients with rectal or endometrial cancer who received EBRT or vaginal brachytherapy (VBT) to the pelvic region, compared with patients treated without RT.[3,4,11] The databases from these large randomized trials were combined to evaluate the long-term probability of developing a second cancer after the primary rectal or endometrial cancer in patients treated with or without pelvic RT.

PATIENTS AND METHODS

Patients and Treatment

In the multicenter TME trial, 1,530 Dutch rectal patients were randomly assigned to preoperative EBRT followed by standardized total mesorectal excision (TME) surgery or TME alone between January 1996 and December 1999. Details of the study design have been described previously.[4,12] Eligible patients had a clinically resectable adenocarcinoma, without evidence of distant metastases, and with an inferior tumor margin below the level of S1/S2 and within 15 cm from the anal verge. Patients allocated to EBRT were treated with a total dose of 25 Gy in five fractions delivered over 5 to 7 days by a three- or four-field technique.[4,12]

In the multicenter PORTEC-1 trial, 715 patients with endometrial adenocarcinoma were enrolled between June 1990 and December 1997. Details of the PORTEC-1 trial have been reported elsewhere.[3,13] All patients underwent total extrafascial hysterectomy with bilateral salphingo-oophorectomy without lymphadenectomy and were randomly assigned to postoperative EBRT or no additional treatment (no RT). Eligible patients had postoperative stage I (according to International Federation of Gynecology and Obstetrics 1988 staging system) endometrial adenocarcinoma and either grade 1 disease with deep (≥ 50%) myometrial invasion, grade 2 disease with any invasion, or grade 3 with superficial (< 50%) invasion. Patients allocated to EBRT were treated with a total dose of 46 Gy in 23 fractions delivered by an anterioposterior opposed-field (30%) or three- or four-field technique (70%).[3,13] The EBRT treatment volume and anatomic region were similar for endometrial and rectal cancers.

In the multicenter PORTEC-2 trial, 427 patients with endometrial cancer were enrolled between May 2002 and September 2006. Details of the PORTEC-2 trial have been reported in previous publications.[11,14] All patients underwent total extrafascial hysterectomy with bilateral salphingo-oophorectomy and were randomly allocated to postoperative EBRT or VBT. Eligible patients had stage I (according to International Federation of Gynecology and Obstetrics 1988 staging system) endometrial carcinoma with high or intermediate risk factors (ie, age ≥ 60 years, with either ≥ 50% myometrial invasion and grade 1 or 2 disease or < 50% invasion and grade 3 disease), or any age with stage IIA disease (except grade 3 disease with > 50% myometrial invasion). Patients assigned to EBRT were treated with a dose of 46 Gy in 23 fractions. Computerized treatment planning was used with a three-dimensional conformal or multiple-field technique, with individual shielding in all fields. For patients assigned to VBT, the upper half of the vagina was treated using a vaginal cylinder. Brachytherapy schedules were as follows: high-dose rate, 21 Gy at 5-mm depth in three fractions of 7 Gy over 2 weeks (87%); low-dose rate, 30 Gy (9%); or medium-dose rate, 28 Gy at 5-mm depth in one session (4%).[11]

An ethics committee approved the design of each trial, and all patients provided informed consent. Because patients in the TME and PORTEC-1 trials were no longer undergoing active follow-up in 2013, the Dutch Pathology Registry of the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA) was used to verify the occurrence of second cancers.[15] When inconsistencies in second cancers were found between data provided by PALGA and the trial database, patients' general practitioners and/or treating hospitals were contacted. Because patients in the PORTEC-2 trial were still undergoing active follow-up in 2013, second cancer incidence in these patients was collected from the trial database. In the Netherlands (and at PALGA), the guidelines for the definition of multiple primaries (ie, second cancers) proposed by the International Association of Cancer Registries and International Agency for Research on Cancer are followed.[16]

Statistical Methods

All data were analyzed by treatment actually received by patients. In the TME trial, 82 (11.4%) of 718 patients assigned to no preoperative RT received (mainly postoperative) EBRT in case of R1 resection, and all 695 patients assigned to EBRT received EBRT. In the PORTEC-1 trial, six (1.7%) of 360 patients assigned to no RT received EBRT, and 15 (4.2%) of 354 patients assigned to EBRT did not receive EBRT. In the PORTEC-2 trial, three (1.4%) and one (0.5%) of 213 patients assigned to VBT received no RT and EBRT, respectively; five (2.3%) and one (0.5%) of 214 patients assigned to EBRT received VBT and no RT, respectively. Median follow-up time was assessed by employing reverse Kaplan-Meier methodology.[17] A competing-risk model with death as a competing event was used to estimate the cumulative incidence (ie, probability) of developing a second primary cancer in the different treatment arms.[18] Gray's test was used to assess the statistical difference between the estimated cumulative incidence of second cancers.[19] Time at risk started at random assignment date and ended at date of occurrence of the first second cancer, death, or last date of study follow-up, whichever occurred first. For subgroups, time at risk ended at date of occurrence of the first second cancer of a specific type, death, or last date of study follow-up. To take the background incidence of cancers in account, data on the Dutch general population provided by the Netherlands Cancer Registry were used.[20] To compare the number of second cancers in the cohort under study with the number of cancers in the Dutch population, standardized incidence ratios (SIRs) were estimated. A Poisson regression model was employed to estimate SIRs and confidence intervals. SIRs were estimated as the ratios of the observed patients' occurrence of first second cancers with the expected occurrence in the Dutch general population, stratified by age, sex, and calendar time. Because basal cell carcinomas are not registered by the Netherlands Cancer Registry, observed basal cell carcinomas in the trials were excluded from the comparison with the general population. Absolute excess risks were calculated as the observed patients' occurrence of second cancers minus the number of expected cancers, divided by person-years at risk and multiplied by 10.000. A two-sided *P* value less than .05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics (version 20.0; SPSS, Chicago, IL). Estimation of SIRs was computed in R (version R-2.15.3; http://www.r-project.org). The Mstate library in R was used for competing-risk analyses.[21,22]

RESULTS

A total of 2,554 patients from the TME (n = 1413), PORTEC-1 (n = 714), and PORTEC-2 (n = 427) trials were analyzed (Fig 1). Overall median follow-up time was 13.0 years (range, 1.8 to 21.2 years): 14.0 years (range, 2.0 to 16.0 years) in the TME trial, 12.6 years (range, 2.8 to 21.2 years) in the PORTEC-1 trial, and 7.5 years (range, 1.8 to 10.5 years) in the PORTEC-2 trial. Table 1 summarizes patient and tumor characteristics. Baseline patient characteristics were equally balanced among the treatment arms in individual studies.[3,4,11]

In the pooled cohort of 2,554 patients, 759 cancers were diagnosed in 549 patients (21.5%). In the TME trial, 306 patients (21.7%) developed a second cancer, compared with 196 (27.5%) in the PORTEC-1 trial and 47 (11.0%) in the PORTEC-2 trial, reflecting the differences in follow-up among the trials. The most common cancers were basal cell carcinomas of the skin (n = 268), followed by breast

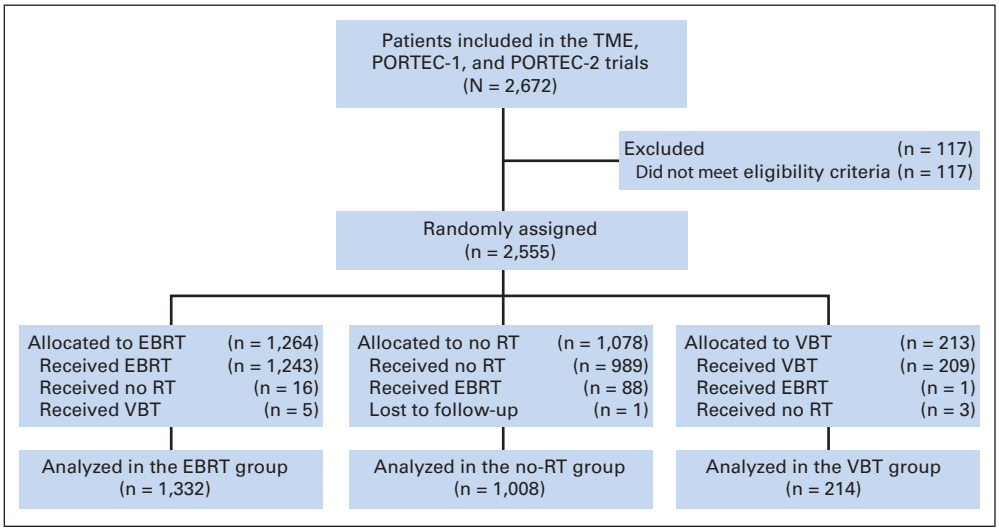

Fig 1. CONSORT diagram. EBRT, external-beam radiotherapy; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; RT, radiotherapy; TME, Total Mesorectal Excision; VBT, vaginal brachytherapy.

(n = 75), lung (n = 55), and colon cancers (n = 52). The distribution of cancer types is listed in Table 2.

No difference in the probability of developing a second cancer was found between the treatment arms (10-year rates: no RT, 15.8%; EBRT, 15.4%; VBT, 14.9%; 15-year rates: no RT, 26.5%; EBRT, 25.6%; $P = .94$; Fig 2A). Similarly, in the individual trials, no differences were found between treatment arms regarding 10-year rates (TME trial: no RT, 15.3% *v* EBRT, 14.8% [Fig 2B]; PORTEC-1 trial: no RT, 16.9% *v* EBRT, 17.3% [Fig 2C]; PORTEC-2 trial: VBT, 14.9% *v* EBRT, 14.4% [Fig 2D]). Similarly, after exclusion of basal cell carcinomas of the skin from the analysis, no statistical significant differences were found. When pooled treatment groups of all studies together were compared, no differences were seen in cumulative incidence of development of a second cancer at a specific site, except for rectosigmoid cancer. However, when excluding the TME patients, there was no statistical difference in rectosigmoid cancer incidence between the treatment arms (10-year rates: VBT, 1.6%; no RT, 0.84%; EBRT, 0.54%; $P = .10$). Specifically, patients who underwent EBRT did not have more second cancers in the abdominal or pelvic area than nonirradiated patients (data not shown).

Table 1. Patient Demographic and Clinical Characteristics

	Total (N = 2,554)		TME (n = 1,413)		PORTEC-1 (n = 714)		PORTEC-2 (n = 427)	
Characteristic	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	66		65		66		69	
Range	23-92		23-92		41-90		49-89	
≤ 60	742	29.1	496	35.1	200	28.0	46	10.8
> 60	1,812	70.9	917	64.9	514	72.0	381	89.2
Sex								
Male	909	35.6	909	64.3	—	—	—	—
Female	1,645	64.4	504	35.7	714	100	427	100
Treatment								
No RT	1,008	39.4	635	44.9	369	51.6	4	0.9
EBRT	1,332	52.2	778	55.1	345	48.3	209	48.9
VBT	214	8.4	—		—	—	214	50.2
TNM stage								
0	25	1.8	25	1.8	—	—	—	—
I	420	29.7	420	29.7	—	—	—	—
II	381	27	381	27	—	—	—	—
III	506	35.8	506	35.8	—	—	—	—
IV	81	5.7	81	5.7	—	—	—	—
FIGO 1998 stage								
IB	329	28.8	—	—	294	41.2	35	8.2
IC	763	66.8	—	—	420	58.8	343	80.3
IIA	49	4.3	—	—	—	—	49	11.5

Abbreviations: EBRT, external-beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; RT, radiotherapy; TME, Total Mesorectal Excision; VBT, vaginal brachytherapy.

Table 2. Second Cancers in Patients in TME, PORTEC-1, and PORTEC-2 Trials

	All Trials						TME Trial				PORTEC-1 Trial				PORTEC-2 Trial					
	EBRT (n = 1,332)		No RT (n = 1,008)		VBT (n = 214)		EBRT (n = 778)		No RT (n = 635)		EBRT (n = 345)		No RT (n = 369)		EBRT (n = 209)		No RT (n = 4)		VBT (n = 214)	
Cancer Type	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any	394	100.0	336	100.0	29	100.0	251	100.0	205	100.0	121	100.0	130	100.0	22	100.0	1	100.0	29	100.0
Hematologic	18	4.6	17	5.1	3	10.3	10	4.0	11	5.4	5	4.1	6	4.6	3	13.6	0	0	3	10.3
Skin	178	45.2	154	45.8	6	20.7	136	54.2	95	46.3	39	32.2	59	45.4	3	13.6	0	0	6	20.7
Breast	31	7.9	38	11.1	6	20.7	3	1.2	10	4.9	24	19.8	27	20.8	4	18.2	1	100	6	20.7
Respiratory	34	8.6	21	6.2	3	10.3	22	8.8	15	7.3	9	7.4	6	4.6	3	13.6	0	0	3	10.3
GI	68	17.3	41	12.2	7	24.1	35	13.9	24	11.7	27	22.3	17	13.1	6	27.3	0	0	7	24.1
Colon	30		22		0		17		14		10		8		3		0		0	
Rectosigmoid	3		4		5		0		0		2		4		1		0		5	
Rectal	6		2		1		1		1		5		1		0		0		1	
Other	29		13		1		17		9		10		4		2		0		1	
Urogenital	50	12.7	45	13.4	2	6.9	35	13.9	41	20.0	13	10.7	4	3.1	2	9.1	0	0	2	6.9
Urinary bladder	19		16		1		10		14		8		2		1		0	0	1	
Prostate	16		16		0		16		16		—		—		—		—		—	
Corpus uteri	3		4		0		3		4		0		0		0		0		0	
Ovarian	2		1		0		1		1		1		0		0		0		0	
Other	10		8		1		5		6		4		2		1		0		1	
Other	15	3.8	20	6.0	2	6.9	10	4.0	9	4.4	4	3.3	11	8.5	1	4.5	0	0	2	6.9

Abbreviations: EBRT, external-beam radiotherapy; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; RT, radiotherapy; TME, Total Mesorectal Excision; VBT, vaginal brachytherapy.

Age and Sex

Although patients age ≤ 60 years at diagnosis of primary cancer in general had a higher second cancer probability than those age > 60 years (15-year rates: 27.2% *v* 23.9%, respectively; $P = .01$), there was no difference in second cancer probability between treatment arms for patients age ≤ 60 years, nor between treatment arms for patients age > 60 years. In addition, no differences in cumulative probability of a second cancer were found between treatment groups in men or women alone (data not shown).

Comparison With General Population

SIR based on all included patients for all types of second cancers was 2.98 (95% CI, 2.82 to 3.14), which results in 154 excess cases per 10.000 patients per year, as compared with a matched general population. SIR based on all patients age ≤ 60 years at diagnosis was 5.47 (95% CI, 4.73 to 6.31), and SIR based on all patients age > 60 years was 2.76 (95% CI, 2.60 to 2.93). All SIR and absolute excess risk values are listed in Table 3.

DISCUSSION

In this pooled analysis of > 2,500 patients with pelvic cancers treated in three large randomized trials, the probability of developing a second cancer was not different between patients treated with or without RT. However, patients treated for rectal or endometrial cancer had a higher probability of developing a second cancer compared with the general population, stratified by age, sex, and calendar time.

Strengths of this pooled analysis of the TME, PORTEC-1, and PORTEC-2 trials are the large group of patients with pelvic cancers (N = 2,554) and the random treatment allocation, ensuring that trial groups were comparable with regard to lifestyle factors, genetic susceptibility, age, and other prognostic factors. Follow-up information of trial patients was complete, and second tumors were verified using the Dutch Pathology Registry.

A possible limitation of the study is the difference in total EBRT dose. The biologic effective dose using α/β 3 was 46 Gy in the PORTEC trials, compared with 40 Gy in the TME trial. No differences were found in development of a second cancer at a specific site or in development of sarcomas. Because the rectum was removed in TME patients, an analysis was performed in which TME patients were excluded. This analysis showed no statistical difference between treatment arms for rectosigmoid cancer, probably because of the smaller sample size. Furthermore, a relatively small number of patients (29%) were age ≤ 60 years at random assignment. In the Dutch population, the incidence of cancer is highest in those between ages 60 and 80 years,[20] which is reflected in this pooled cohort, with the majority of patients age > 60 years (71%), making it a representative cohort for this analysis.

The occurrence of a second cancer has also been analyzed in other randomized trials.[7,8] Patients with rectal cancer in the Uppsala trial and Swedish rectal cancer trial were treated with pre- or postoperative EBRT or surgery alone. In these trials, more second cancers developed in the EBRT group (stratified relative risk [RR], 1.85; 95% CI, 1.23 to 2.78), and an increased risk of a second cancer was found in the irradiated group for organs in or near the irradiated volume (stratified RR, 2.04; 95% CI, 1.10 to 3.79). Actuarial life-table procedures were used to calculate the cumulative proportion of second cancers.[7] In another randomized controlled trial, 568 patients with stage I endometrial cancer were randomly allocated to VBT followed by EBRT or VBT alone. An increased risk of a second cancer was found after EBRT (hazard ratio [HR], 1.42; 95% CI, 1.01 to 2.00), and an even higher risk was found in women treated with EBRT who were age < 60 years at

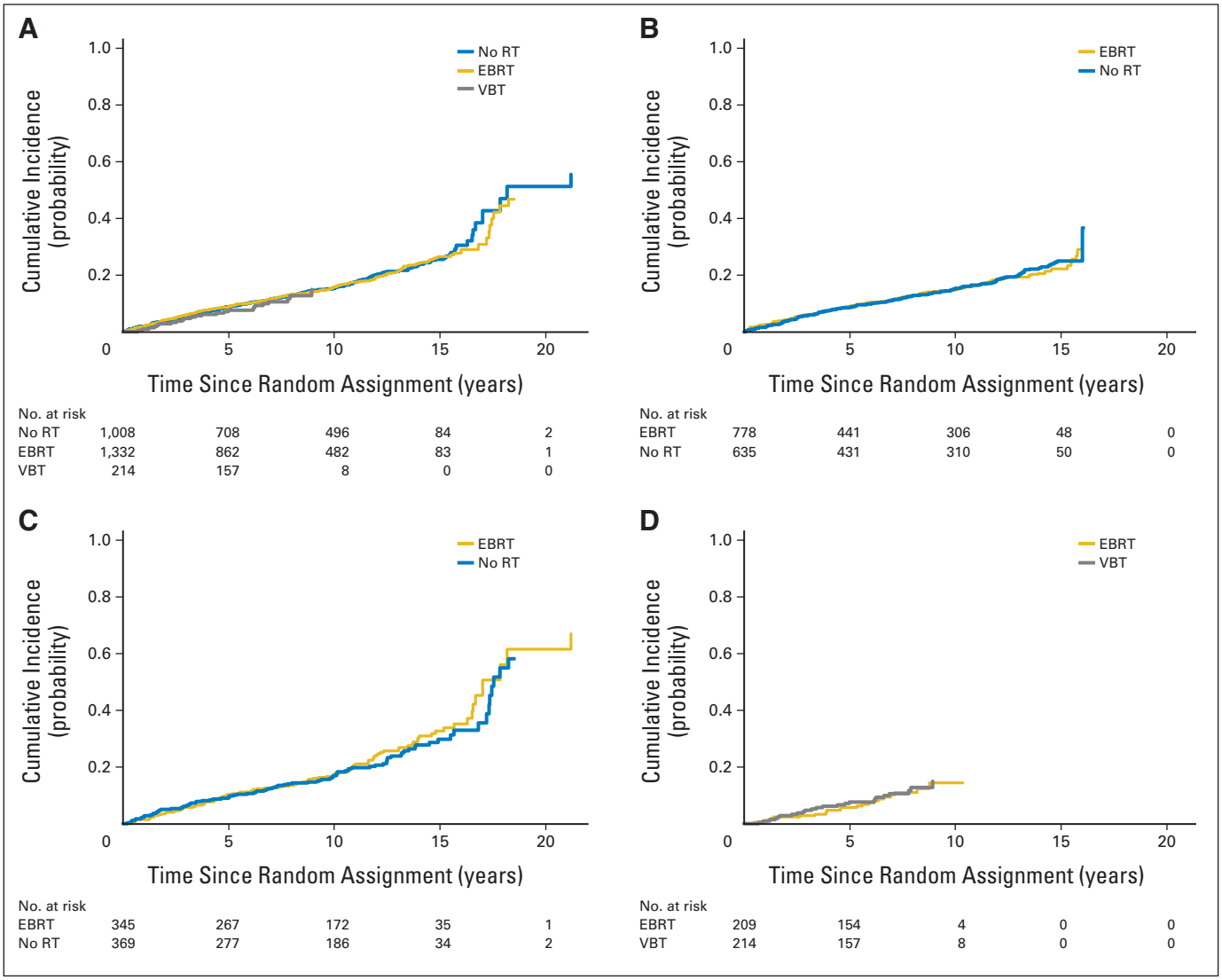

Fig 2. Cumulative probability of developing second cancer in (A) all, (B) TME (Total Mesorectal Excision), (C) PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1), and (D) PORTEC-2 trials. NOTE. Because only four patients were included in no-RT group in the PORTEC-2 trial, these patients are not represented in panel D. EBRT, external-beam radiotherapy; RT, radiotherapy; VBT, vaginal brachytherapy.

diagnosis (HR, 2.02; 95% CI, 1.30 to 3.15).[8] In this analysis, in which actuarial life-table procedures were also used, death was not taken into account as a competing event. Therefore, the probability of developing a second cancer was overestimated because of the number of patients who died before experiencing a second cancer.[23] Other nonrandomized studies have used competing-risk models to analyze the incidence of second cancers. In a retrospective cohort study, data from 69,739 patients with endometrial cancer from the US SEER cancer registries were used. Patients treated with EBRT developed more second cancers compared with patients treated without RT ($P < .001$), especially colon ($P < .001$), rectal ($P = .017$), bladder ($P < .001$), vaginal ($P < .04$), and soft tissue cancers ($P = .014$). Patients receiving VBT only showed an increased risk for a second cancer of the urinary bladder ($P = .006$).[10] Another large SEER study evaluated the association between RT and second cancers in 90,502 patients with endometrial cancer. The RR for developing a second cancer after RT was 1.25 (95% CI, 1.20 to 1.29), and an increased risk of developing a second cancer was found in the radiation field and after a longer latency period (> 10 years).[24] In contrast, a different study, which used the US SEER registries to evaluate the association between RT and second cancers in patients with primary rectal cancer, did not find a significant difference between irradiated (n = 5,641) and nonirradiated patients (n =

Table 3. SIRs for All Types of Second Cancer*

Characteristic	Observed	Expected	SIR	95% CI	AER†
All patients	449	151	2.98	2.82 to 3.14	154
Male sex	167	52	3.23	2.98 to 3.50	178
Female sex	282	101	2.78	2.58 to 3.00	140
Age ≤ 60 years	121	22	5.47	4.73 to 6.31	151
Age > 60 years	328	119	2.76	2.60 to 2.93	163

Abbreviations: AER, absolute excess risk; SIR, standardized incidence ratio.
*Excluding basal cell carcinomas.
†Per 10,000 persons per year.

15,269; HR, 1.02; 95% CI, 0.92 to 1.12). Irradiated patients seemed to have a significantly decreased rate of second cancers of the prostate and breast, whereas the rates for cancers of the urinary bladder, uterine corpus, and cervix were increased.[9] Finally, a SEER registry–based study of 647,672 patients with different primary cancers found an increased RR of developing a second cancer after treatment with RT. RRs were highest for organs that received > 5 Gy and increased with longer follow-up time and younger age at diagnosis of the first primary cancer. However, it was estimated that only 8% of the second cancers in irradiated patients might have been related to RT, compared with other factors, such as lifestyle factors, genetic susceptibility, and chemotherapy.[2]

This finding of only a small proportion of second cancers being attributable to RT might explain why our randomly assigned EBRT and VBT groups did not develop significantly more second cancers than patients treated without RT. Furthermore, several studies we have cited found an increasing risk when follow-up time increased. Our follow-up time did not go beyond 20 years after diagnosis of the primary cancer. However, because the median age of our patients was 66 years at diagnosis, the clinical relevance of an even longer follow-up time is limited. Furthermore, in contrast to studies using the SEER registries, with selection and treatment biases, we investigated the incidence of second cancers in randomized controlled trials for which it could be safely assumed that all treatment groups were equal with regard to lifestyle factors and genetic susceptibility, which may not be the case in retrospective cohort studies.

SIRs found in our study suggest that these patients with rectal or endometrial cancer had a 3× higher probability of developing a second primary cancer, as could be expected based on the incidence of cancer in a sex- and age-matched general Dutch population. For patients age ≤ 60 years at diagnosis, this probability even increased to 5.5×. This higher risk of developing a second cancer is most likely caused by several etiologic factors, such as lifestyle, environment, and host factors and interactions and other influences (eg, gene-environment and gene-gene interactions).[25] Etiologic factors involved in the development of a primary cancer probably also contribute to the development of a second cancer. For instance, patients could be more susceptible to primary and secondary cancers because of inherited or acquired genetic factors, like mutations in mismatch repair genes, *TP53*, or the Wnt signaling pathway, or because of Lynch syndrome. However, both for rectal and endometrial cancers, it is estimated that only 1% to 5% of cancers in unselected patient groups are related to Lynch syndrome. Therefore, the impact of Lynch syndrome on the overall burden of second cancers in this cohort is limited. Furthermore, lifestyle factors may also contribute to the development of cancers (eg, increased body-mass index is associated with increased risk for rectal, endometrial, and several other cancers).[26]

In conclusion, in this large pooled cohort of > 2,500 patients from randomized trials with a median follow-up of 13.0 years, no increased risk of developing a second cancer was found in patients who underwent pelvic EBRT, which is important for counseling and shared decision making. In addition, both patients and physicians should be aware during follow-up that rectal and endometrial cancer survivors have a 3× higher risk of developing a second primary cancer compared with the general population, with basal cell skin, breast, lung, and colon cancers being most common.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials

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